PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 March 2001 (19.03.01)	
International application No. PCT/DK00/00387	**Applicant's or agent's file reference** 584
International filing date (day/month/year) 11 July 2000 (11.07.00)	**Priority date** (day/month/year) 16 July 1999 (16.07.99)
Applicant OTTOSEN, Erik, Rytter	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

03 February 2001 (03.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Claudio Borton

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
584		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK00/00387	11/07/2000	16/07/1999
International Patent Classification (IPC) or national classification and IPC C07C275/40		
Applicant LEO PHARMACEUTICAL PRODUCTS LTD. A/S ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/02/2001	18.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Heibl, C Telephone No. +49 89 2399 8331

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00387

I. Basis f th report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-30	as originally filed				

Claims, No.:

1-9	as received on	25/06/2001	with letter of	20/06/2001	

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 8,9.

because:

   ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-7
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7

No: Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R S ction III----------

The subject-matter of claims 8 and 9 is directed to a therapeutic method for treating the human or animal body. Under the terms of Rule 67.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination of such claims.

Re Section V----------

The compounds as claimed in amended claim 1 (formula I) are characterized by having at least one substituent R_1, the substituent R_2 and the urea group -NH-CO-NH-Q-Y in the ortho position of the corresponding phenyl ring to said substituents/groups are bound. The present compounds may thus be regarded as novel over the disclosure of the prior art document WO 98/32730 (D1) (Art. 33(2) PCT).

By way of comparative tests it has been shown, that selected compounds of the present invention exhibit similar pharmacological activities (inhibition of the production of IL-1β, TNF-α and PMN-superoxide) *in vitro*, as compared to structurally closely related compounds disclosed in D1, but, surprisingly, show an improved biological activity *in vivo* with respect to the inhibition of LPS induced TNF-α production in mice, as well as a markedly increased absorption in ip administration (applicant's letter of 20.06.01).
For the subject-matter claimed, the presence of an inventive step may thus be acknowledged as well (Art. 33(3) PCT.

Re Section VII----------

The comparative compound "ref. a)" in Table 1 on page 9 is not compound 106 disclosed in PCT/DK/98/00008 = D1. Cpd. 106 is a benzo nitrile derivative.

The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.

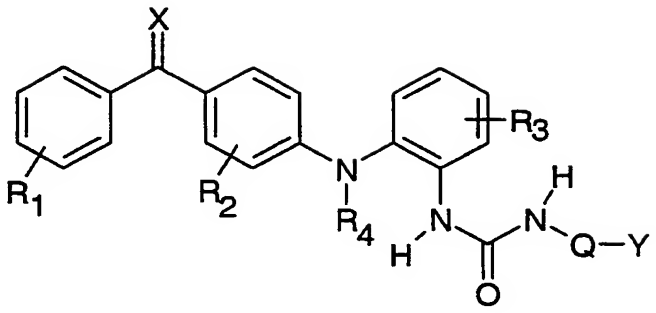
R Secti n VIII----------

As highlighted in the applicant's letter of 20.06.01 the amended claim 1 now requires that at least one substituent **R1** and the substituent **R2** (one only present) be in **ortho position**. That means that the meaning of R2 = H, which is still contained in amended claim 1 (cf. *"...said substituent being selected from the group consisting of hydrogen..."*), are no longer reasonable and, therefore, have to be deleted.

Claim 1 is unclear with respect to the passage "or Y represents a group of formula -(Z-O)$_n$-Z, where Z is a (C_1-C_3)alkyl and n is a integer $\geq$ 1, and no continuos linear sequence of atoms in the group Y exceeds 15". Amendment is necessary (Art. 6 PCT).

CLAIMS

1. A compound of the formula I



I

wherein R_1 independently represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, carbamoyl, phenyl and nitro, provided that when R_1 represents one substituent, it is in the ortho position, and when R_1 represents more than one substituent, at least one R_1 substituent is in the ortho position; R_2 is one substituent in the ortho position, said substituent being selected from the group consisting of hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, carbamoyl, phenyl and nitro;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

R_4 represents hydrogen, (C_1-C_3)alkyl, or allyl;

Q represents a bond, -SO_2-, or -C(R_6)(R_7)(-O-C=O)-, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or (C_1-C_4)alkyl;

Y represents (C_1-C_{15})alkyl, (C_2-C_{15})olefinic group, (C_3-C_{10})carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represented by the formula R_5; or Y represents a group of

formula $-(Z-O)_n-Z$, where Z is a (C_1-C_3)alkyl and n is an integer > 1, and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, (C_1-C_4)alkyl, amino, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, nitro, -COOH, $-CONH_2$, -CONHR', or -CONRR' wherein R and R' stands for (C_1-C_3)alkyl;

X represents oxygen or sulphur,

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

2. A compound according to claim 1 wherein independently

- R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, or cyano.

- R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy.

- R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, cyano, or carboxy.

- R_4 represents hydrogen, (C_1-C_2)alkyl, or allyl.

- X represents oxygen.

- Q represents a bond or $-SO_2-$.

- Y represents (C_1-C_6)alkyl; (C_2-C_6)alkenyl; (C_3-C_6)cycloalkyl; (C_5-C_8)cycloalkene group; or phenyl; any of which is optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5, R_5 representing fluoro, chloro, bromo, hydroxy, amino, (C_1-C_2)alkoxy, (C_1-C_4)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, -COOH, -$CONH_2$, -CONHR', or -CONR'R' wherein R' represents (C_1-C_2)alkyl.

3. A compound according to any one of the preceding claims wherein R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

4. A compound according to any one of the preceding claims wherein R_1 is methyl and R_2 is Cl.

5. A compound according to claim 1 selected from the group consisting of
1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103),
1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109),
1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino] phenyl]urea (Compound 112),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]urea (Compound 117),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 121),
1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 123),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]urea (Compound 124),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 125),
1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 126),
and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

6. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 5 together with a pharmaceutically acceptable carrier and optionally together with a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

7. Use of a compound according to any one of claim 1 to 5 for the preparation of a medicament for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne.

8. A method for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne, characterised in administering to a patient suffering from at least one of said diseases an effective amount of one or more compounds according to any one of claims 1 to 5 as an active ingredient alone, or if necessary together with a pharmaceutically acceptable carrier, and, optionally, a second active ingredient optionally selected from the

group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

9. A method of treatment according to the preceding claim comprising administering to a mammal in need of systemic treatment a suitable dose of a compound of formula I of from 0.1 to 200 mg/kg bodyweight, preferably a dose of from 0.2 to 50 mg/kg of mammal bodyweight one or more times daily.

ENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 584	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/DK 00/00387	International filing date *(day/month/year)* 11 July 2000	(Earliest) Priority Date *(day/month/year)* 16 July 1999
Applicant LEO PHARMACEUTICAL PRODUCTS LTD. A/S		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (See Box I).

2. [ ] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the **title**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. --
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIO SEARCH REPORT

ational application No.
PCT/DK00/00387

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9 and 10
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00387

Claim 9 and 10 are directed to a method for treatment of the human or animal body by therapy methods practised on the human or animal body, see Rule 39.1 (iv).
Nevertheless, a search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00387

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 275/40, A61K 31/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9832730 A1 (LEO PHARMACEUTICAL PRODUCTS LTD A/S), 30 July 1998 (30.07.98) -- --------	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 Sept 2000	10. 10. 2000
Name and mailing address of the International Searching Authority European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel(+31-70)340-2040, Tx 31 651 epo nl, Fax(+31-70)340-3016	Authorized officer GÖRAN KARLSSON/GH Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

SA 291620

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/06/00

International application No.
PCT/DK 00/00387

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9832730 A1	30/07/98	AU 2969297 A	05/01/98
		AU 5478198 A	18/08/98
		CN 1248966 T	29/03/00
		EP 0902872 A	24/03/99
		EP 0966424 A	29/12/99
		GB 9701453 D	00/00/00
		PL 334806 A	13/03/00

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05751 A1

(51) International Patent Classification[7]: C07C 275/40, A61K 31/17

(21) International Application Number: PCT/DK00/00387

(22) International Filing Date: 11 July 2000 (11.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/144,062 16 July 1999 (16.07.1999) US

(71) Applicant *(for all designated States except US)*: LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØVENS KEMISKE FABRIK PRODUKTIONSAKTIESELSKAB) [DK/DK]; Industriparken 55, DK-2750 Ballerup (DK).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: OTTOSEN, Erik, Rytter [DK/DK]; Lotusvej 6, DK-3650 Ølstykke (DK).

(74) Agent: THALSØ-MADSEN, Birgit; Patent Dept., Leo Pharmaceutical Products Ltd. A/S, Industriparken 55, DK-2750 Ballerup (DK).

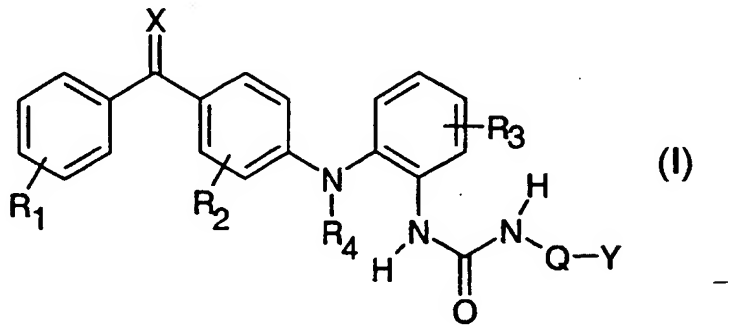
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α



(I)

(57) Abstract: The present invention relates to compounds of formula (I) wherein R_1 and R_2 independently represent one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro; R_2 further being represented by hydrogen; R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl; R_4 represents hydrogen, (C_1-C_3)alkyl or allyl; Q represents a bond, -SO_2-, or -$C(R_6)(R_7)$(-O-C=O)-, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or (C_1-C_4)alkyl; Y represents (C_1-C_{15})alkyl, (C_2-C_{15})olefinic group, (C_3-C_{10})carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represnet by the formula R_5; or Y represents a group of formula -$(Z\text{-}O)_n$-Z, where Z is a (C_1-C_3)alkyl, and n is an integer >1, and no continuous linear sequence of atoms in the group Y exceeds 15; R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, (C_1-C_4)alkyl, amino, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, nitro, -COOH, -$CONH_2$, -CONHR' or -CONRR' wherein R et R' stands for (C_1-C_3)alkyl; X represents oxygen or sulfur, or a pharmaceutically acceptable salt thereof, or a hydrate or solvate threof. The compounds are valuable in the human and veterinary therapy.

WO 01/05751 A1

AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α

FIELD OF THE INVENTION

This invention relates to a hitherto unknown class of compounds which shows anti-inflammatory effects, to pharmaceutical preparations containing these compounds, to dosage units of such preparations, and to their use in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis and atopic dermatitis, uveitis, septic shock, AIDS, and acne.

BACKGROUND OF THE INVENTION

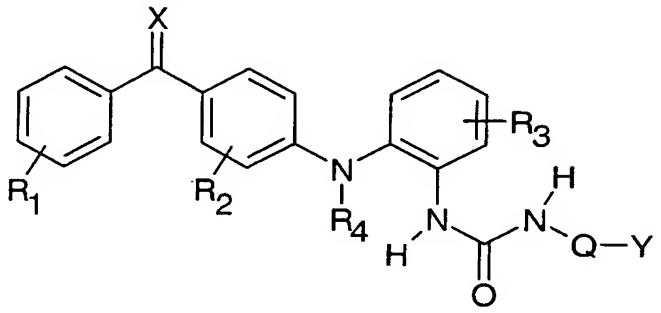
Previously, a series of closely related aminobenzophenones (e.g. 4-(2-amino-4-nitrophenylamino)benzophenone) have been described (Hussein, F.A. *et al*, Iraqi J. Sci., 22, 54-66 (1981)). However, there is no description of their uses. PCT/DK98/00008 discloses aminobenzophenone inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor a (TNF-α) secretion *in vitro*, said compounds being potentially useful for treatment of inflammatory diseases in which the production of cytokines is involved in the pathogenesis, e.g. asthma, rheumatoid arthritis, psoriasis, contact dermatitis, and atopic dermatitis. Furthermore the compounds of PCT/DK98/00008 was tested *in vivo* for anti-inflammatory properties in the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model, (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, Agents Action, 37, (1992); Stanley, P.L. et al, Skin Pharmacol, 4, 262-271 (1991)). In this chronic skin inflammation model the compounds had the same potency compared to the reference compound hydrocortisone.

The purpose of the present invention is to provide further pharmacologically active aminobenzophenone derivatives and related compounds.

This purpose is achieved with the novel aminobenzophenone derivatives according to the general formula I that are potent inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) secretion *in vitro*, making them potentially useful for treatment of inflammatory diseases, in which the secretion and regulation of cytokines or more specifically interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) are involved in the pathogenesis. The inhibition or down regulation of the cytokines is possibly due to an inhibition of MAP kinases.

SUMMARY OF THE INVENTION

The compounds of the present invention are represented by the general formula I below



I

wherein R_1 and R_2 independently represent one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro; R_2 further being represented by hydrogen;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)-alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

R_4 represents hydrogen, (C_1-C_3)alkyl, or allyl;

Q represents a bond, -SO_2-, or -C(R_6)(R_7)(-O-C=O)-, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or (C_1-C_4)alkyl;

Y represents (C_1-C_{15})alkyl, (C_2-C_{15})olefinic group, (C_3-C_{10})carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represented by the formula R_5; or Y represents a group of formula -$(Z\text{-}O)_n$-Z, where Z is a (C_1-C_3)alkyl and n is an integer > 1, and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, (C_1-C_4)alkyl, amino, (C_1-

C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, nitro, -COOH, -$CONH_2$, -CONHR', or -CONRR' wherein R and R' stands for (C_1-C_3)alkyl;

X represents oxygen or sulphur,

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

Preferred embodiments of the invention:

In compounds of the invention it is preferred that R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxy-carbonyl, or cyano; R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy; R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, cyano, or carboxy; R_4 represents hydrogen, (C_1-C_2)alkyl, or allyl; X represents oxygen; Q represents a bond. or -SO_2-; Y represents (C_1-C_6)alkyl; (C_2-C_6)alkenyl; (C_3-C_6)cycloalkyl; (C_5-C_8)cycloalkene group; or phenyl; any of which is optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5 as defined below, and R_5 represents fluoro, chloro, bromo, hydroxy, amino, (C_1-C_2)alkoxy, (C_1-C_4)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, -COOH, -$CONH_2$, -CONHR', or -CONR'R' wherein R' represents (C_1-C_2)alkyl.

More preferred are compounds of formula I wherein R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy; preferably R_1 is methyl and most preferrably 2-methyl; R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy; preferably R_2 is Cl and most preferably 2-Cl; preferably R_3 represents hydrogen, methyl, methoxy, fluoro, chloro, or bromo; R_4 represents hydrogen; Y represents (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, or

phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, amino, azido, (C_1-C_3)alkyl, (C_1-C_2)alkoxycarbonyl, cyano, -COOH, -$CONH_2$, and $CON(CH_3)_2$.

Most preferably Y represents methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, cyclohexyl, hexyl, 6-chloro-hexyl, -$(CH_2)_2COOCH_2CH_3$, $(CH_2)_2COOH$, tolyl, or phenyl.

Further preferred compounds of general formula I are compounds wherein R_1, R_2, and R_3 represent one substituent. R_1 and R_2 preferably being in the ortho position.

Specific compounds of the invention includes:
1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103),
1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(4-methylphenylsulfonyl)urea (Compound 105),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(phenylsulfonyl)urea (Compound 106),
1-*tert*-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 107),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109),
1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110),
Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionate (Compound 111),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 112),
3-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionic acid (Compound 113),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-*N*-methyl-phenylamino]-5-fluoro-phenyl]urea (Compound 115),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 116),

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]urea (Compound 117),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 118),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 119),
1-Ethyl-3-[5-bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 120),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 121),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]urea (Compound 122),
1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 123),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]urea (Compound 124),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 125),
1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 126),
and salts thereof with pharmaceutically acceptable acids, hydrates or solvates thereof.

As used in the specification, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to any univalent group derived from an alkane by removal of a hydrogen atom from any carbon atom, and includes the subclasses of normal alkyl (*n*-alkyl), and primary, secondary and tertiary alkyl groups respectively, and having the number of carbon atoms specified, including for example (C_1-C_3)alkyl, (C_1-C_4)alkyl, (C_5)alkyl, (C_5-C_{15})alkyl, (C_6-C_{10})alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and t-butyl. Alkane refers to an acyclic branched or unbranched hydrocarbon having the general formula C_nH_{2n+2}, and therefore consisting entirely of hydrogen atoms and saturated carbon atoms.

"Olefinic group" refers to a straight or branched acyclic hydrocarbon having one or more carbon-carbon double bonds of either E or Z stereochemistry where applicable, and having the number of carbon atoms specified. The term includes, for example, (C_2-C_{15})olefinic

group, preferably a (C_2-C_{15})alkenyl; (C_2-C_3)olefinic group, preferably a (C_2-C_3)alkenyl; vinyl; allyl; 1- butenyl; 2-butenyl; and 2-methyl-2-propenyl. Olefinic groups having only one carbon-carbon double bond, herein called alkenyl, are preferred.

"Alkoxy" refers broadly to a radical of the formula -OR, where R is alkyl as defined above, for example (C_1-C_3)alkoxy, (C_1-C_2)alkoxy, methoxy, ethoxy, n-propoxy, and the like.

"(C_1-C_3)alkylthio" refers broadly to a radical of the formula -SR, where R is alkyl as defined above and includes methylthio, ethylthio, n-propylthio, and 2-propylthio.

"(C_1-C_6)alkylamino" refers broadly to a radical of the formula -NHR or -NR_2, where R is alkyl as defined above having from 1-6 carbon atoms and includes, for example, methylamino, dimethylamino, di-(n-propyl)amino, and n-butyl(ethyl)amino.

"(C_1-C_3)alkoxycarbonyl" refers broadly to a radical of the formula -COOR, where R is alkyl as defined above and includes methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, and i-propoxycarbonyl.

"(C_3-C_{10})monocyclic hydrocarbon group" includes the saturated cycloalkanes and unsaturated cyclic olefins, such as cycloalkenes having one endocyclic double bond, and having from 3-10 carbon atoms, and includes, for example, (C_3-C_8)cycloalkyl, cyclopropyl, cyclopentyl, cyclohexyl, and cyclooctyl, (C_3-C_{10})cycloalkene group, and (C_3-C_8)cycloalkene group. Specific examples are cycloprop-2-enyl, cyclobut-2-enyl, cyclopent-2-enyl, cyclohex-3-enyl, and cyclonon-4-enyl.

"Amino" means the group -NH_2.

"Carbamoyl" refers to any one of the groups -$CONH_2$, -CONHR, and -CONRR' where R and R' represent alkyl as defined above.

"Carboxy" refers to a radical of the formula -COOH.

"Halogen" means the same or different of fluoro, chloro, bromo, and iodo; fluoro, chloro, and bromo being preferred.

The phenyl group of R_1 and R_2 may optionally be substituted, e.g. with hydroxy; amino;

nitro; cyano; halogen, preferably fluoro, chloro, or bromo; methyl; or methoxy.

The compounds can be used in the form of their salts which are formed with pharmaceutically acceptable inorganic or organic acids, such as hydrochloric, hydrobromic and hydroiodic acid, phosphoric acid, sulphuric acid, nitric acid, p-toluenesulphonic acid, methanesulphonic acid, formic acid, acetic acid propionic acid, citric acid, tartaric acid, succinic acid, benzoic acid, maleic acid, these examples being considered as non-limiting for the invention.

Pharmacological methods

To study the effect of the compound of the present invention in vitro the inhibition of the IL-1β and TNF-α secretion was measured using the following procedure:

Cytokine production was measured in the media from lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells. The mononuclear cells were isolated from human peripheral blood by Lymphoprep® (Nycomed, Norway) fractionation and suspended in RPMI 1640 (growth medium) with foetal calv serum (FCS, 2%), at a concentration of 5 x 10^5 cells/ml. The cells were incubated in 24-well tissue culture plates in 1 ml aliquots. Test compounds were dissolved in dimethylsulfoxide (DMSO, 10 mM) and were diluted with the medium. Compounds were added to the cells for 30 minutes, then LPS (1 mg/ml final concentration) was added. The plates were incubated for 18 hours, and the concentration of IL-1β and TNF-α in the medium was determined by enzyme-linked immunosorbent assays. The median inhibitory concentrations (IC_{50}) of the compounds were calculated. The results are shown in Table 1 below.

The compounds of the present invention also show similar activities in the ability to inhibit PMN (polymorphonuclear) superoxide secretion which is also indicative of potentially useful anti-inflammatory drugs. The compounds were tested using the following procedure:

Human polymorphonuclear (PMN) granulocytes were isolated from human blood by dextran sedimentation, Lymphoprep® fractionation and hypotonic lysis of contaminating erythrocytes.

Superoxide anion generation was measured as the superoxide dismutase inhibitable reduction of ferricytochrome C (Madhu, S.B. et al, Inflammation, 16, 241, (1992)). The cells were suspended in Hanks' balanced salt solution, and incubated for 10 minutes at

37°C with test compounds. The cells were primed by the addition of TNF-α (3 ng/ml final concentration) for 10 minutes, and then ferricytochrome C, (final concentration 750µg/ml), bovine serum albumin (BSA, final concentration 1 mg/ml) and formyl-methionyl-leucyl-phenylalanine (fMLP, final concentration 10^{-7} M) were added for 3 minutes. The cells were chilled on ice, and were spun down. The optical densities in the cell-free supernatant was measured in a spectrophotometer. The median inhibitory concentration (IC_{50}) of the compounds was calculated. The results are shown in Table 1.

Table 1.	Inhibition of cytokines and PMN-superoxide production in vitro by compounds of the present invention.		
	The median inhibition concentration (IC_{50}, nM) of		
Comp No.; Ex. No.	IL-1β	TNF-α	PMN-superoxide
101, Ex. 1	13	5.0	4.0
102, Ex. 2	22	2.2	13
114, Ex. 14	7.9	3.2	4.0
ref. a)	13	7.1	5.0
ref. b)	>1000	631	316

ref. a): 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone, compound 106 disclosed in PCT/DK98/00008. ref. b): 1-Ethyl-3-[2-(4-benzoyl-phenylamino)phenyl]urea of the general formula I in PCT/DK98/00008.

These results show that the compounds of the present invention are able to inhibit the production of IL-1β, TNF-α and PMN-superoxide showing pharmacological activities comparable to compounds of the prior art, thus making them potentially useful in the treatment of inflammatory diseases.

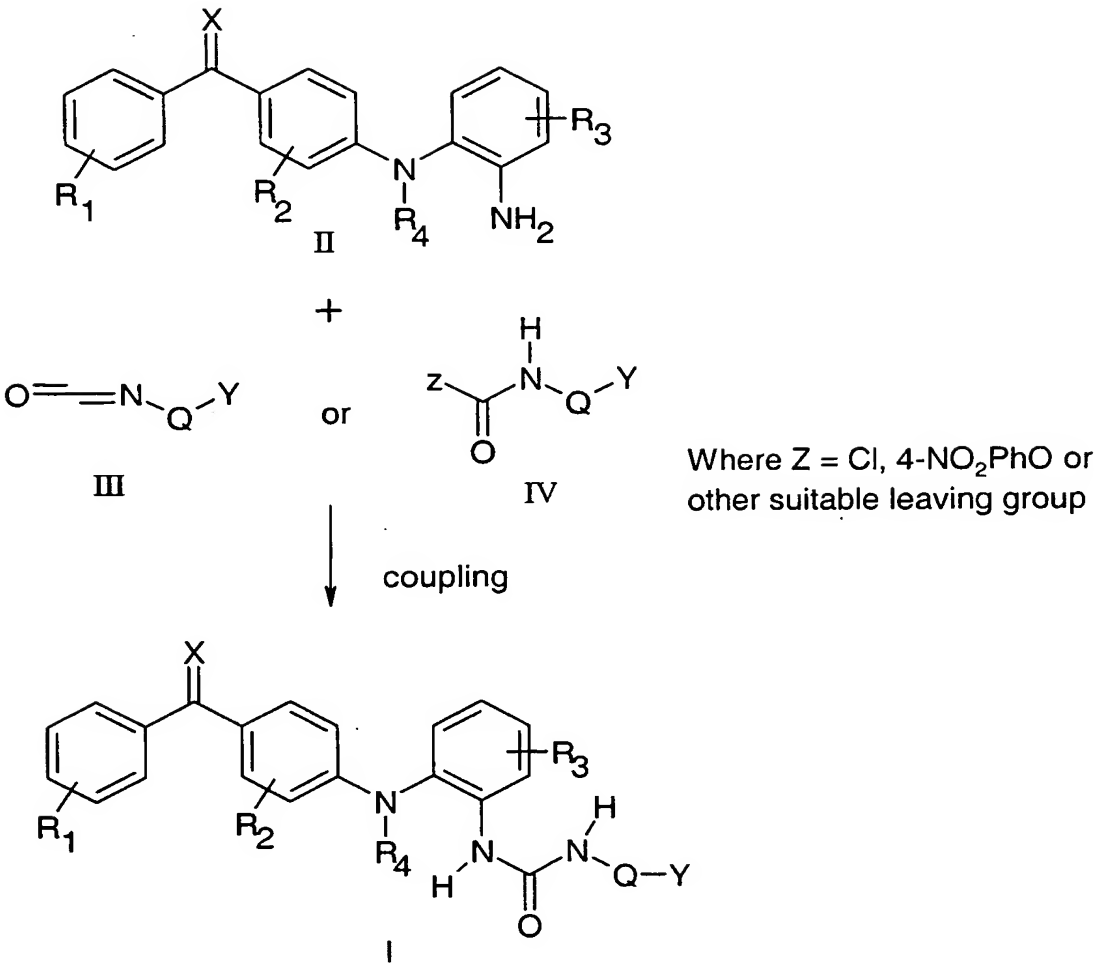
To study the compounds of the present invention *in vivo* the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model can be used (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, Agents Action, 37, (1992); Stanley, P.L. et al, Skin Pharmacol, 4, 262-271 (1991)), cf. description of method in PCT/DK98/00008 hereby incorporated by reference. These results shows that the compounds of the present invention are of the same potency compared to known reference compounds, e.g. hydrocortisone with its known side effects, whereas the compounds of the present

invention are well tolerated and are non-toxic. Some members of the present class of compounds show a very low absorption, thus making them especially useful in the treatment of various dermatological diseases. In general, they may be administered by e.g. oral, intravenous, intranasal, topically or transdermal routes.

Method of preparation

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. The compounds of the present invention can be synthesised using the methods outlined below, together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The novel compounds of formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognised by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the educt molecule must be compatible with the reagents and reactions proposed. Not all compounds of formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods can be used.

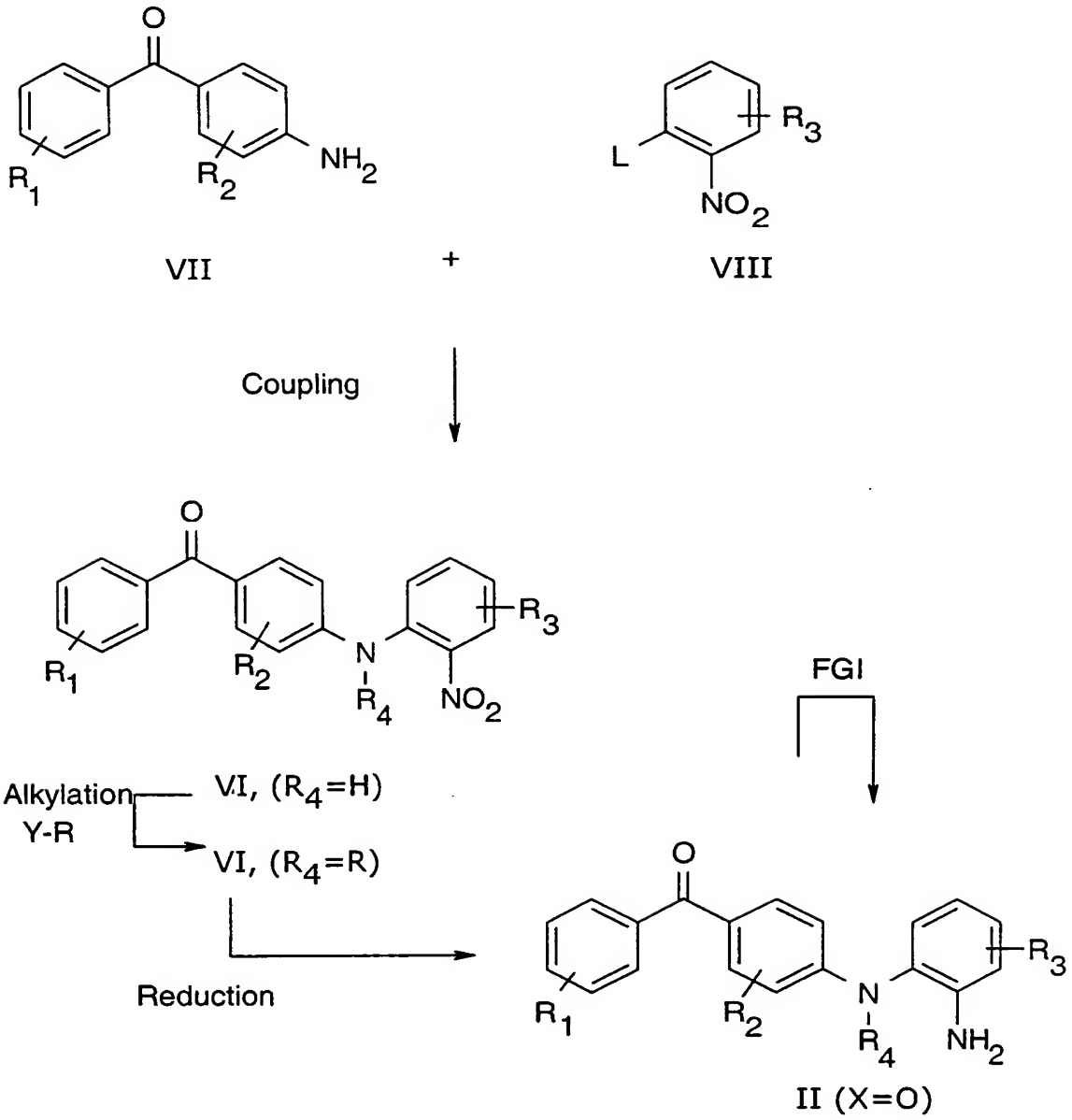
Compounds according to the present invention may be prepared by a process comprising coupling of an amine of the formula II with an isocyanates of the formula III or a suitable activated derivative with the formula IV; e.g. carbamic acid chlorides and carbamic acid esters (phenoxy, 4-nitrophenoxy and 2,4,5-trichlorophenoxy) or other suitable activated derivatives of the formula IV, as shown in scheme 1, where R_1, R_2, R_3, R_4, Q, X, and Y are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed.



and R_1, R_2, R_3, R_4, X, Q, and Y have the above meanings.

Scheme 1

Compounds accordingly to the present invention with the general formula II(X=O) may be prepared by several methods known to those skilled in the art of organic synthesis. One useful sequence is shown in scheme 2 were the key process comprising coupling of an amine of the formula VII with an fluoride, chloride, bromide, iodide, or triflate with the formula VIII, as shown in Scheme 2, where R_1, R_2, R_3, and, R_4 are as defined in general formula I, to give a coupled product with the general formula VI, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed. This compound VI may then be reduced to the corresponding amine with the general formula II by treatment with standard reducing agents. Examples of such reducing agents include, but are not limited to, stannous chloride dihydrate; hydrogen, ammonium formiate, or hydrazine hydrate and a catalytic amount of palladium on carbon.



L: Br, I, OSO_2CF_3, or F and Cl

Y:Cl, Br, I, OSO_2CF_3 , OSO_2CH_3, or OTs

FGI: Functional group interconversion

and R_1, R_2, R_3, and R_4 have the above meanings.

Scheme 2

The coupling reaction is carried out using any of the methods for the formation of diphenylamines known to one skilled in the art of organic synthesis. The preferred method is the nucleophilc aromatic substiution method which comprising coupling of an amine with an arylfluoride or arylchloride in the presence of a base, in an suitable solvent. Especially

potassium-*tert*-butoxide (KO*t*-Bu), sodium-*tert*-butoxide (NaO*t*-Bu), sodium hydrid (NaH), and potassium hydride (KH) have proven to be the best bases in this process, but other bases may be used as well.

The reaction is typically performed at ambient temperature (20-25 ^{o}C) in dipolar aprotic solvents like dimethylsulfoxide (DMSO), dimethylformamide (DMF), or *N*-methylpyrrolidone (NMP) under an inert atmosphere like argon or nitrogen.

Alternatively, the coupling reaction can be done by the palladium catalysed amination method which comprising coupling of an amine with an arylhalogenide (iodide, bromide, triflate, or in some cases chloride) in the presence of a base, a suitable Pd source, and a suitable phosphine ligand in an inert solvent.

The palladium compound used in the process is not particularly limited, and as specific examples are

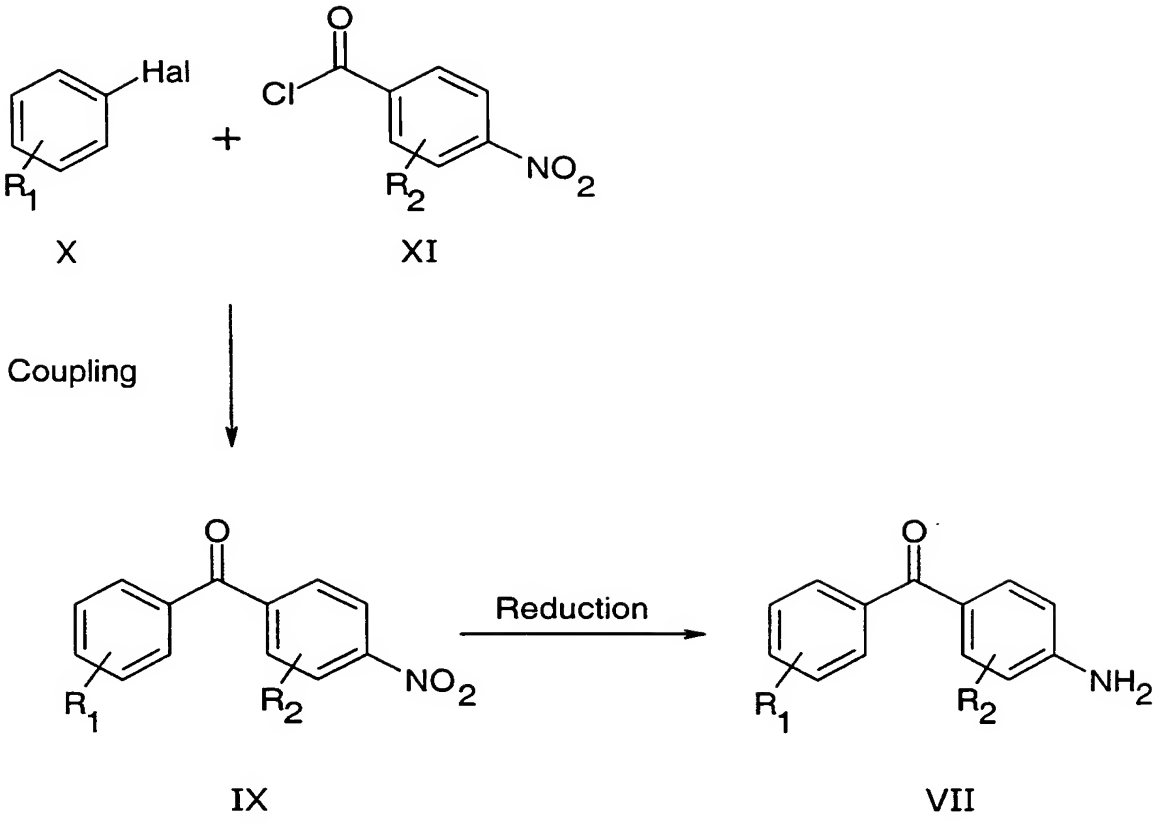
palladium(II) acetate, palladium(II) chloride, palladium(II) bromide, dichlorobis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0). The preferred ligand include, but are not limited to, racemic or non-racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter referred to as BINAP), tri-o-tolylphosphine, tri-tert-butylphosphine, 1,1'-bis(diphenylphosphino)-ferrocene, bis[(2-diphenylphosphino)phenyl]ether (DPEphos), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl, 2-(di-*tert*-butylphosphino)biphenyl, and 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos). The amount of palladium and ligand used in this process is typically in the range 0.1 to 10 % by mole relative to the amount of the aromatic halide (or triflate) used. Especially sodium-*tert*-butoxide (NaO*t*-Bu) and caesium carbonate (Cs_2CO_3) have proven to be the best bases in this process, but other bases may be used as well. The reaction is typically performed at elevated temperature (80-120 ^{o}C) in inert solvents like 1,4-dioxane, toluene, benzene and tetrahydrofurane under an inert atmosphere like argon or nitrogen.

Compounds according to the present invention in which R_4 is not hydrogen may be prepared by a process comprising coupling of an amine of the formula VI (R_4= H) with an alkylating agent, as shown in scheme 2, where R_1, R_2, R_3, and, R_4 are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected before the coupling reaction is performed and subsequently removed.

Typically alkylating agents of the general formula R-Y include, but are not limited to, iodides (Y=I), bromides (Y=Br), chlorides (Y=Cl) and sulfonates ($Y=OSO_2R'$, where R' represents methyl, trifluoromethyl or 4-methylphenyl).

Compounds according to the present invention may in special cases be prepared by a simple functional group interconversion (FGI), meaning a standard process, known to those skilled in the art of organic synthesis, where a functional group in compounds with the general formula I (or any other intermediate described herein) is transformed into a different functional group in one or more synthetic steps, leading to a new compound with the general formula I. Examples of such processes are, but are not limited to, hydrolysis of an ester to give an acid under basic conditions; deprotection of an methylether to give an phenol by treatment with e.g. borontribromide (BBr_3); and catalytic hydrogenation of an olefin to give an saturated hydrocarbon.

Compounds according to the present invention in which C=X represents -(CS)- may be prepared from compounds of the invention (or any other intermediate described herein) in which C=X represents -(CO)- by a process using an appropiate thiocarbonylating agent such as phosphorous pentasulfide (P_4S_{10}), or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide) or the like.



hal: Br, I

and R_1, and R_2 have the above meanings.

SCHEME 3

Compounds accordingly to the present invention with the general formula VII may be prepared by several methods known to those skilled in the art of organic synthesis. One useful sequence is shown in Scheme 3. The key step comprises coupling of a bromide (or iodide) with the general formula X with an acid chloride with the general formula XI to afford the benzophenone with the general formula IX. This compound IX may then be reduced to the corresponding amine with the general formula VII by treatment with standard reducing agents. Examples of such reducing agents include, but are not limited to, stannous chloride dihydrate; hydrogen, ammonium formiate, or hydrazine hydrate and a catalytic amount of palladium on carbon. The coupling reaction is done by transforming the bromide (X) into a reactive organometallic intermediate, e.g. by treatment with butyllithium to afford the lithium derivative or by treatment with magnesium to afford the magnesium derivative. The reactivity of this intermediate is then modulated by transme-

tallation to e.g. zinc, by treatment with $ZnCl_2$, $ZnBr_2$, or ZnI_2. This organozinc compound is then coupled with the acid chloride, with the general formula XI, under the influence of a palladium(0) complex in catalytic amount. Examples of such catalyst include but are not particularly limited to tetrakis(triphenylphosphine)palladium(0), tetrakis(triphenylarsine)-palladium(0), dichlorobis(triphenylphosphine)palladium(II), or benzylchlorobis(triphenylphosphine)palladium(II).

It may be more advantageous in some cases to alter the sequence of the processes described above. The described sequence of processes is not considered as being limited for the preparation of the compounds of the present invention with the general formula I and alteration of the reaction sequence is an obvious alternative for those skilled in the art of organic synthesis.

The present compounds are intended for use in pharmaceutical compositions which are useful in the treatment of the above mentioned diseases.

The amount required of a compound of formula I (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. A suitable dose of a compound of formula I for systemic treatment is 0.1 to 200 mg/kg bodyweight, the most preferred dosage being 0.2 to 50 mg/kg of mammal bodyweight, administered one or more times daily.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 0.1% to 100% by weight of the formulation.

Conveniently, dosage units of a formulation contain between 0.07 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 20% by weight of the formulation but the active ingredient may comprise as much as 50% w/w. Formulations suitable for nasal or buccal administration may comprise 0.1% to 20% w/w. for example about 2% w/w of active ingredient.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The formulations, both for veterinary and human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), transdermal, intra-articular, topical, nasal, or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be administered in the form of a bolus, electuary or paste.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema. Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or

semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations, such as aerosols and atomizers.
In addition the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients.

The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

The novel compounds of the invention are of value in the human and veterinary practice as systemic and topical therapeutic agents for the treatment and prevention of diseases. The novel compounds show anti-acne properties and, i.a., anti-inflammatory and cytokine regulating effects possibly due to MAP kinase inhibition, and are useful in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondylo-arthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, and osteoporosis.

The invention will now be further described in the following general procedures, preparations and examples:

EXAMPLES

General procedures, preparations and examples

The exemplified compounds I are listed in table 2. All melting points are uncorrected. For ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra (300 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified, for deuteriochloroform and hexadeuterodimethylsulfoxide solutions relative to internal tetramethylsilane (δ 0.00) or chloroform (^{1}H NMR δ 7.25, ^{13}C NMR δ 76.81). The value for a multiplet (m), either defined (doublet (d), triplet (t), quartet (q)) or not at the approximate mid point is given unless a range is quoted (s singlet, b broad). The organic solvents used were anhydrous. The term

"chromatography" refers to column chromatography using the flash technique and was performed on silica gel.

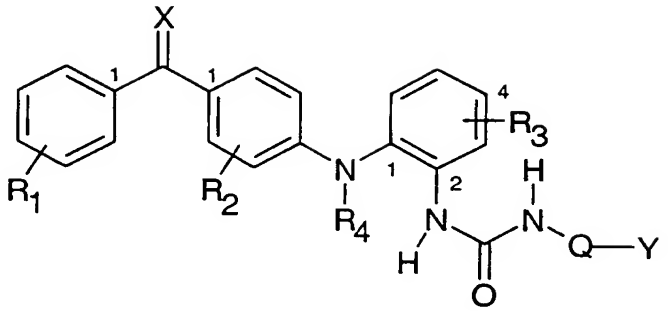
The following abbreviations have been used throughout:

AgOAc	Silver acetate
BTC	Bis(trichloromethyl) carbonate
$CDCl_3$	Deuteriochloroform
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Hexadeuterodimethylsulfoxide
Et_3N	Triethylamine
EtOAc	Ethyl acetate
Et_2O	Diethylether
HMPA	Hexamethylphosphorous triamide
NMM	*N*-Methylmorpholine
THF	Tetrahydrofurane
TLC	Thin layer chromatography

Table 2 Compounds of general formula I

Comp. No.	Example No	X	R_1	R_2	R_3	R_4	Q	Y
101	1	O	2-Me	2-Cl	H	H	Bond	-cyclohexyl
102	2	O	2-Me	2-Cl	H	H	Bond	$-CH_2CH_3$
103	3	O	2-Me	2-Cl	H	H	Bond	-phenyl
104	4	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_3CH_3$
105	5	O	2-Me	2-Cl	H	H	$-(SO_2)-$	-tolyl
106	6	O	2-Me	2-Cl	H	H	$-(SO_2)-$	-phenyl
107	7	O	2-Me	2-Cl	H	H	Bond	$-C(CH_3)_3$
108	8	O	2-Me	2-Cl	H	H	Bond	$-CH(CH_3)_2$
109	9	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_2CH_3$
110	10	O	2-Me	2-Cl	H	H	Bond	$-CH_3$
111	11	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_2COOCH_2CH_3$
112	12	O	2-Me	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
113	13	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_2COOH$
114	14	O	2-Me	2-Cl	4-F	H	Bond	$-CH_2CH_3$
115	15	O	2-Me	2-Cl	4-F	CH_3	Bond	$-CH_2CH_3$
116	16	O	2-Me, 4-Bu	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
117	17	O	2-Me, 5-Me	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
118	18	O	2-Me, 3-Cl	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
119	19	O	2-Me, 4-OEt	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
120	20	O	2-Me	2-OEt	4-Br	H	Bond	$-CH_2CH_3$
121	21	O	2-Me, 4-Cl	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
122	22	O	2-Me, 3-Me	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
123	23	O	2-Me, 4-OMe	2-F	4-Br	H	Bond	$-CH_2CH_3$
124	24	O	2-Me, 4-Me, 5-Me	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
125	25	O	2-Me, 4-F	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
126	26	O	2-Me	2-F	4-Br	H	Bond	$-CH_2CH_3$

The numbering in Table 2 refers to the numbering in the formula below



General procedure 1: Coupling of compounds of the general formula II with compounds of the general formula III to give compounds of the general formula I , or a protected derivative thereof.

To a solution or suspension of an amine (1.0 mmol), with the general formula II, in an inert solvent (10 ml, typically toluene, pyridine or EtOAc) was slowly added an isocyanate (1.1-2.5 mmol), with the general formula III. Stirring was continued at room temperature for 24 h or until the starting material had disappeared as seen on TLC. The reaction mixture was concentrated *in vacuo* to afford the crude product. The crude product was typically either purified by chromatography and/or crystallized to give the title compound.

Example 1

1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Cyclohexyl isocyanate

Solvent for the reaction: EtOAc

Purification: Chromatography using EtOAc/hexane 1:1 as eluant followed by trituration from Et_2O

Mp: 154-155 °C

^1H NMR (DMSO-d_6): δ 8.34 (s,1H), 8.05 (d,1H), 7.76 (s,1H), 7.41 (m,1H), 7.35-7.10 (m,6H), 6.95 (m,1H), 6.68 (m,2H), 6.57 (m,1H), 3.44 (m,1H), 2.29 (s,3H), 1.77 (m,2H), 1.63 (m,2H), 1.52 (m,1H), 1.40-1.00 (m,5H)

Example 2

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate
Solvent for the reaction: Pyridine
Purification: The title compound crystallized on the addition of water to the reaction mixture. Filtration, washing (water), and drying afforded a pure crystalline product.

Mp: 158.3-159.8 °C

^{1}H NMR (DMSO-d_6): δ 8.34 (s,1H), 8.04 (d,1H), 7.79 (s,1H), 7.42 (m,1H), 7.10-7.34 (m,6H), 6.96 (m,1H), 6.67 (m,2H), 6.57 (m,1H), 3.07 (m,2H), 2.29 (s,3H), 1.02 (t,3H)

Example 3

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103)

General procedure: 1, except the reaction mixture was heated to 100 °C for 4 h
Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone
Starting compound III: Phenyl isocyanate
Solvent for the reaction: Pyridine
Purification: Crystallization from Et_2O

Mp: 163-166.8 °C

^{1}H NMR (DMSO-d_6): δ 9.15 (s,1H), 8.43 (s,1H), 8.13 (s,1H), 8.09 (d,1H), 7.10-7.50 (m,11H), 7.05 (m,1H), 6.96 (m,1H), 6.75 (d,1H), 6.63 (dd,1H), 2.28 (s,3H)

Example 4

1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104)

General procedure: 1, except the reaction mixture was heated to 100 °C for 4 h
Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone
Starting compound III: Butyl isocyanate
Solvent for the reaction: Toluene
Purification: Chromatography using EtOAc/pentane 3:7 as eluant followed by crystallization from Et_2O

Mp: 104-106 °C

^{1}H NMR (DMSO-d_6): δ 8.35 (s,1H), 8.04 (d,1H), 7.80 (s,1H), 7.41 (m,1H), 7.08-7.34 (m,6H), 6.97 (m,1H), 6.70 (t,1H), 6.66 (d,1H), 6.57 (dd,1H), 3.05 (m,2H), 2.29 (s,3H), 1.20-1.40 (m,4H), 0.86 (t,3H)

Example 5

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(4-methylphenylsulfonyl)urea (Compound 105)

General procedure: 1
Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone
Starting compound III: p-Toluenesulfonyl isocyanate
Solvent for the reaction: Toluene
Purification: The product was filtered off and washed with Et_2O to afford the title compound.

Mp: 180-185 °C

^{13}C NMR (DMSO-d_6): δ 195.3, 150.3, 149.0, 143.9, 139.1, 136.7, 136.4, 133.9, 133.4, 133.4, 131.0, 130.7, 129.5, 129.3, 129.2, 128.8, 127.2, 126.4, 126.3, 125.6, 125.5, 124.1, 120.5, 114.7, 111.4, 20.9, 19.7

Example 6

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(phenylsulfonyl)urea (Compound 106)

General procedure: 1
Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone
Starting compound III: Benzenesulfonyl isocyanate
Solvent for the reaction: Toluene
Purification: The product was filtered off and washed with Et_2O to afford the title compound.

Mp: 196-201 °C

^{13}C NMR (DMSO-d_6): δ 195.3, 150.3, 139.6, 139.1, 136.4, 133.8, 133.7, 133.4, 131.7, 131.0, 130.7, 130.3, 129.3, 129.0, 128.8, 128.4, 127.2, 126.4, 126.4, 125.6, 125.5, 124.1, 120.5, 116.3, 114.7, 111.4, 19.7

Example 7

1-*tert*-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 107)

General procedure: 1, except the reaction mixture was heated to 50 °C for 6 h
Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone
Starting compound III: *tert*-Butyl isocyanate
Solvent for the reaction: Pyridine
Purification: The title compound crystallized on the addition of water to the reaction mixture. Filtration, washing (water), and drying afforded a pure crystalline product.

Mp: 159-161 °C

^{1}H NMR (DMSO-d_6): δ 8.32 (s,1H), 8.05 (d,1H), 7.73 (s,1H), 7.07-7.46 (m,7H), 6.95 (m,1H), 6.67 (d,1H), 6.60 (s,1H), 6.57 (dd,1H), 2.29 (s,3H), 1.26 (s,9H)

Example 8

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: *iso*-Propyl isocyanate

Solvent for the reaction: Toluene

Purification: Chromatography using EtOAc/pentane 3:7 as eluant followed by crystallization from water

Mp: 103-106 °C

^{1}H NMR (DMSO-d_6): δ 8.34 (s,1H), 8.07 (d,1H), 7.74 (s,1H), 7.42 (m,1H), 7.10-7.35 (m,6H), 6.95 (m,1H), 6.66 (m,2H), 6.56 (dd,1H), 3.71 (m,1H), 2.29 (s,3H), 1.06 (d,6H)

Example 9

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Propyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from Et_2O

Mp: 133-135 °C

^{13}C NMR (DMSO-d_6): δ 195.2, 155.1, 150.7, 139.4, 136.3, 136.2, 133.5, 130.9, 130.5, 128.6, 128.3, 126.1, 125.8, 125.5, 121.8, 120.3, 114.7, 111.4, 40.8, 22.8, 19.6, 11.3

Example 10

1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Methylisocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from Et_2O

Mp: 154-155 °C

^{1}H NMR (DMSO-d_6): δ 8.35 (s,1H), 8.01 (d,1H), 7.84 (s,1H), 7.40 (m,1H), 7.09-7.35 (m,6H), 6.97 (m,1H), 6.68 (d,1H), 6.59 (m,2H), 2.61 (d,3H), 2.29 (s,3H)

Example 11

Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionate (Compound 111)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl 3-isocyanatopropionate

Solvent for the reaction: Pyridine

Purification: Chromatography using EtOAc/pentane 3:2 as eluant to give the title compund as a syrupy

^{13}C NMR ($CDCl_3$): δ 196.7, 172.9, 156.3, 148.8, 139.2, 137.8, 135.0, 133.6, 133.0, 131.9, 131.3, 130.9, 129.6, 128.5, 125.4, 125.4, 124.2, 123.8, 116.4, 112.7, 60.9, 36.0, 34.7, 20.4, 14.1

Example 12

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 112)

General procedure: 1

Starting compound II: 4-[(2-Amino-4-bromo-phenyl)amino]-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of EtOAc/pentane 1:1

Mp: 125-127 °C

^{13}C NMR ($CDCl_3$): δ 197.5, 155.8, 149.2, 138.9, 137.7, 135.2, 135.0, 133.6, 131.4, 131.2, 129.8, 129.7, 128.2, 126.8, 126.2, 125.5, 125.0, 118.7, 116.1, 112.3, 35.2, 20.5, 15.2

Example 13

3-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionic acid (Compound 113)

Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido) propionate (Compound 111, 6.25 mmol) and K_2CO_3 (9.4 mmol) was stirred in a mixture of MeOH (25 ml) and water (8 ml) for 4 h at ambient temperature. More water (13 ml) was added and

the reaction mixture was stirred overnight. The reaction mixture was poured into EtOAc and water. pH was adjusted to approximately 4 with glacial acetic acid. The organic phase was separated, washed with water and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a weakly coloured oily crude product. Purification was done by chromatography using CH_2Cl_2/MeOH/CH_3COOH 250:10:1 as eluant to afford the title compound.

^{13}C NMR ($CDCl_3$): δ 197.5, 176.3, 157.0, 148.9, 138.9, 137.9, 134.9, 133.5, 132.8, 131.7, 131.3, 131.1, 129.8, 128.4, 125.6, 125.5, 124.4, 123.9, 116.3, 112.6, 35.8, 34.5, 20.7, 20.5

Example 14

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114)

General procedure: 1

Starting compound II: 2-Chloro-4-[(4-fluoro-2-aminophenyl)amino]-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Chromatography using EtOAc/pentane 1:2 as eluant to give the title compound as an syrupy

^{13}C NMR ($CDCl_3$): δ 197.2, 162.9, 159.6, 155.1, 150.2, 138.9, 137.8, 137.4, 137.2, 135.1, 133.6, 131.4, 131.1, 129.7, 128.4, 128.0, 127.9, 125.5, 124.7, 115.6, 111.8, 110.1, 109.8, 108.2, 107.9, 35.2, 20.5, 15.1

Example 15

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-*N*-methyl-phenylamino]-5-fluoro-phenyl]urea (Compound 115)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromo-*N*-methyl-phenylamino)-2-chloro-2'-methylbenzophenone

Purification: Chromatography using EtOAc/pentane 1:5 as eluant

^{13}C NMR ($CDCl_3$): δ 197.6, 162.2, 154.8, 152.8, 139.4, 138.8, 137.1, 135.4, 133.9, 31.3, 130.9, 129.6, 129.0, 128.5, 126.3, 125.5, 114.9, 111.1, 109.3, 107.1, 39.4, 34.9, 20.3, 14.8

Example 16

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-*n*-butyl-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 116)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-4'-*n*-butyl-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

^{13}H NMR (DMSO-d_6): δ 8.36 (m, 1H), 8.27 (s, 1H), 7.94 (s, 1H), 7.24 (d, 1H), 7.2-7.0 (m, 5H), 6.86 (t, 1H), 6.69 (d, 1H), 6.58 (dd, 1H), 3.08 (m, 2H), 2.59 (t, 2H), 2.32 (s, 3H), 1.56 (m, 2H), 1.30 (m, 2H), 1.15-0.80 (m, 6H)

Example 17

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]urea (Compound 117)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2',5'-dimethylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 195.5, 154.8, 150.3, 139.2, 138.1, 134.7, 133.6, 133.5, 133.4, 131.4, 131.0, 129.1, 127.8, 127.4, 126.5, 124.2, 121.9, 118.4, 115.1, 111.6, 33.9, 20.4, 19.4, 15.2

Example 18

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(3-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 118)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2,3'-dichloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 193.8, 154.6, 151.0, 142.3, 138.0, 134.5, 134.4, 134.1, 133.2, 130.7, 127.9, 127.2, 127.0, 126.5, 124.9, 124.1, 121.9, 118.6, 115.2, 111.5, 33.8, 16.6, 15.1

Example 19

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-ethoxy-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 119)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-4'-ethoxy-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 194.5, 160.8, 154.8, 149.6, 140.6, 138.0, 132.9, 132.5, 132.3, 130.6, 128.2, 127.8, 127.6, 124.2, 121.9, 118.2, 117.3, 114.7, 111.8, 111.1, 63.3, 33.9, 20.8, 15.2, 14.6

Example 20

1-Ethyl-3-[5-bromo-2-[3-ethoxy-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 120)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-ethoxy-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 195.2, 160.2, 154.7, 151.9, 143.1, 137.4, 134.2, 132.3, 129.9, 128.6, 128.3, 127.1, 126.3, 125.0, 124.1, 122.2, 118.0, 117.5, 106.6, 97.2, 62.9, 33.8, 19.2, 15.1, 13.5

Example 21

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 121)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2,4'-dichloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 194.1, 154.6, 150.6, 139.0, 138.0, 135.1, 133.6, 133.5, 130.6,

130.4, 127.8, 127.2, 125.9, 125.6, 124.1, 121.8, 118.4, 114.9, 111.6, 45.0, 33.8, 19.4, 15.1

Example 22

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,3-dimethylbenzoyl)-phenylamino]phenyl]urea (Compound 122)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-2',3'-dimethylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 195.6, 154.6, 150.5, 140.3, 138.0, 137.4, 134.2, 134.0, 133.7, 131.5, 127.8, 127.2, 126.0, 125.6, 125.1, 124.1, 121.8, 118.4, 115.1, 111.4, 33.8, 19.6, 16.0, 15.1

Example 23

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 123)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-fluoro-4'-methoxy-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 192.0, 162.3, 160.8, 154.8, 152.2, 138.9, 138.0, 133.1, 132.3, 131.1, 127.8, 127.6, 124.2, 122.0, 118.4, 116.6, 116.4, 110.7, 109.8, 100.1, 55.3, 33.9, 20.2, 15.2

Example 24

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]urea (Compound 124)

General procedure: 1

Starting compound II: 4'-(2-Amino-4-bromophenylamino)-2'-chloro-2,4,5-trimethylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 195.2, 154.7, 149.9, 139.6, 137.9, 136.4, 134.2, 133.2, 133.0, 132.4, 130.3, 127.6, 127.5, 127.1, 124.1, 121.8, 118.2, 114.8, 111.6, 33.8, 19.4, 19.2, 18.6, 15.1

Example 25

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 125)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-chloro-4'-fluoro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 194.1, 162.9, 154.6, 150.3, 140.4, 138.0, 135.6, 133.3, 131.6, 127.7, 127.3, 126.4, 124.1, 121.8, 118.3, 117.7, 114.8, 112.4, 111.6, 33.8, 19.8, 15.1

Example 26

1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 126)

General procedure: 1

Starting compound II: 4-(2-Amino-4-bromophenylamino)-2-fluoro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of 1,2-dichloroethane/hexane

^{13}C NMR (DMSO-d_6): δ 192.9, 163.0, 154.8, 153.0, 140.7, 138.0, 135.0, 133.3, 130.6, 129.9, 128.0, 127.2, 125.5, 124.2, 122.0, 118.6, 115.5, 109.9, 100.1, 33.9, 19.3, 15.2

Example 27. Tablet containing compound 102

Compound 102 (active substance)	50 mg
Lactose	125 mg
Starch	12 mg
Methyl cellulose	2 mg
Sodium carboxymethyl cellulose	10 mg
Magnesium stearate	1 mg

The active substance, lactose and starch are mixed to a homogeneous state in a suitable mixer and moistened with a 5 per cent aqueous solution of methyl cellulose 15 cps. The mixing is continued until granules are formed. If necessary, the wet granulation is passed through a suitable screen and dried to a water content of less than 1% in a suitable drier, e.g. fluid bed or drying oven. The dried granules are passed through a 1 mm screen and mixed to a homogeneous state with sodium carboxymethyl cellulose. Magnesium stearate is added, and the mixing is continued for a short period of time. Tablets with a weight of 200 mg are produced from the granulation by means of a suitable tabletting machine.

Example 28. Formulation for injection containing compound 102.

Compound 102 (active substance)	1%
Sodium chloride	q.s.
Ethanol	10%
Water for injection to make	100%

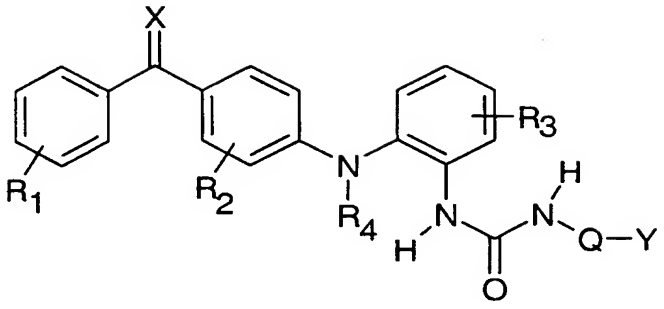
The active substance is dissolved in ethanol (10%) then water for injection made isotonic with sodium chloride is added to make 100%. The mixture is filled into ampoules and sterilized.

Example 29. Cream formulation containing compound 101.

Compound 101 (10 g) was dissolved in Octyldodecyl myristate (250g) to form Part A. Methylparaben (1 g) and propylparaben (0.2 g) were dissolved in phenoxyethanol (6 g) and mixed with a 0.025 M Phosphate buffer pH = 7.5 (632,8 g) to form Part B. Cetostearyl alcohol (50 g) and ARLACEL 165® (50 g) was melted in a vessel at 70° to 80 °C. Part A was added and heated to 60-70°C. The aqueous phase was likewise heated to 60-70 °C and slowly added to the melted oil phase under high speed stirring. The homogenized components were cooled to room temperature.

CLAIMS

1. A compound of the formula I



I

wherein R_1 and R_2 independently represent one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro; R_2 further being represented by hydrogen;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

R_4 represents hydrogen, (C_1-C_3)alkyl, or allyl;

Q represents a bond, -SO_2-, or -C(R_6)(R_7)(-O-C=O)-, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or (C_1-C_4)alkyl;

Y represents (C_1-C_{15})alkyl, (C_2-C_{15})olefinic group, (C_3-C_{10})carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represented by the formula R_5; or Y represents a group of formula -$(Z\text{-}O)_n$-Z, where Z is a (C_1-C_3)alkyl and n is an integer > 1, and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, (C_1-C_4)alkyl, amino, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, nitro, -COOH, -$CONH_2$, -CONHR', or -CONRR' wherein R and R' stands for (C_1-C_3)alkyl;

X represents oxygen or sulphur,

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

2. A compound according to claim 1 wherein independently

- R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, or cyano.

- R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy.

- R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, cyano, or carboxy.

- R_4 represents hydrogen, (C_1-C_2)alkyl, or allyl.

- X represents oxygen.

- Q represents a bond or -SO_2-.

- Y represents (C_1-C_6)alkyl; (C_2-C_6)alkenyl; (C_3-C_6)cycloalkyl; (C_5-C_8)cycloalkene group; or phenyl; any of which is optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5, R_5 representing fluoro, chloro, bromo, hydroxy, amino, (C_1-C_2)alkoxy, (C_1-C_4)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, -COOH, -$CONH_2$, -CONHR', or -CONR'R' wherein R' represents (C_1-C_2)alkyl.

3. A compound according to any one of the preceding claims wherein R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro,

bromo, hydroxy, methyl, or methoxy.

4. A compound according to any one of the preceding claims wherein one or both of R_1 and R_2 represent one substituent, said substituent preferably being in the ortho position.

5. A compound according to any one of the preceding claims wherein R_1 is methyl and R_2 is Cl.

6. A compound according to claim 1 selected from the group consisting of
1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103),
1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109),
1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 112),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,5-dimethylbenzoyl)-phenylamino]phenyl]urea (Compound 117),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-chloro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 121),
1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(4-methoxy-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 123),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2,4,5-trimethylbenzoyl)-phenylamino]phenyl]urea (Compound 124),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(4-fluoro-2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 125),
1-Ethyl-3-[5-bromo-2-[3-fluoro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 126),
and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

7. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 6 together with a pharmaceutically acceptable carrier and optionally together with a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

8. Use of a compound according to any one of claim 1 to 7 for the preparation of a medicament for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne.

9. A method for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne, characterised in administering to a patient suffering from at least one of said diseases an effective amount of one or more compounds according to any one of claims 1 to 7 as an active ingredient alone, or if necessary together with a pharmaceutically acceptable carrier, and, optionally, a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

10. A method of treatment according to the preceding claim comprising administering to a mammal in need of systemic treatment a suitable dose of a compound of formula I of from 0.1 to 200 mg/kg bodyweight, preferably a dose of from 0.2 to 50 mg/kg of mammal bodyweight one or more times daily.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00387

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 275/40, A61K 31/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9832730 A1 (LEO PHARMACEUTICAL PRODUCTS LTD A/S), 30 July 1998 (30.07.98) -- --------	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 Sept 2000	10.10.2000

Name and mailing address of the International Searching Authority
European Patent Office P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel(+31-70)340-2040. Tx 31 651 epo nl.
Fax(+31-70)340-3016

Authorized officer
GÖRAN KARLSSON/GH
Telephone No.

INTERNATIONAL SEARCH REPORT

Int :tional application No.
PCT/DK00/00387

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9 and 10
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK00/00387

Claim 9 and 10 are directed to a method for treatment of the human or animal body by therapy methods practised on the human or animal body, see Rule 39.1 (iv).
Nevertheless, a search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/06/00

Inter. ..ional application No.
PCT/DK 00/00387

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9832730 A1	30/07/98	AU 2969297 A	05/01/98
		AU 5478198 A	18/08/98
		CN 1248966 T	29/03/00
		EP 0902872 A	24/03/99
		EP 0966424 A	29/12/99
		GB 9701453 D	00/00/00
		PL 334806 A	13/03/00